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PW 246936

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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re application of

Ryuji UENO

Serial No. 60/132,009

Filed April 30, 1999

For : AGENT FOR TREATING DRY EYE

Group Art Unit

Examiner

**TRANSLATOR'S DECLARATION**

Honorable Commissioner of Patents and Trademarks  
Washington, D.C. 20231

Sir:

I, Ritsuko Arimura, declare:

That I am well acquainted with both the Japanese and English languages;

That the attached document represents a true English translation of US Patent Application Serial No. 60/132,009 filed on April 30, 1999; and

That I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed this 12th day of November, 1999.

*Ritsuko Arimura*  
Ritsuko Arimura

PATENT APPLICATION SERIAL NO. \_\_\_\_\_

U.S. DEPARTMENT OF COMMERCE  
PATENT AND TRADEMARK OFFICE  
FEE RECORD SHEET

/07/1999 MOLIVER 00000027 60132009

FC:114	150.00 OP
FC:139	130.00 OP

PTO-1556  
(5/87)

\*U.S. GPO: 1988-433-214/80404

**SPECIFICATION**  
**AGENT FOR TREATING DRY EYE**  
**TECHNICAL FIELD OF THE INVENTION**

The present invention relates to an agent for treating dry eye.

5

**BACKGROUND ART**

One of the symptoms of ophthalmic diseases drawing much attention these days is dry eye. The dry eye is defined to mean a condition wherein lacrimal fluid is less in amount or abnormal in quality, with or without the presence of corneal and conjunctival lesion (Yamada, M., et al., Folia Ophthalmol. Jpn., 43, 1289-1293 (1992)). Specific symptoms include dry eye observed in  
10 hypolacrimation, alacrima, xerophthalmia, Sjögren syndrome, keratoconjunctivitis sicca, Stevens-Johnson syndrome, ocular pemphigus, marginal blepharitis, diabetes and the like, dry eye observed after cataract operation, that in conjunction with allergic conjunctivitis and the like, and dry eye  
15 due to hypolacrimation caused by increased VDT (visual display terminal) work, dry room with air conditioning and the like.

The dry eye is caused by various reasons that may not be necessarily clear, but, at the moment, a drastic treatment method such as an improvement of less secretion of lacrimal fluid has not been established yet. Therefore, dry eye is  
20 diagnosed according to subjective symptoms obtained by questioning and objective symptoms based on Schirmer test, corneal and conjunctival staining test and the like, and treated by increasing the lacrimal fluid reservoir in conjunctival sac, thereby to alleviate subjective symptoms of patients and to protect the eyes from drying, and the like.

25 For the above-mentioned therapy, instillation of chondroitin sulfate, methyl cellulose and the like, and internal use of bromhexine hydrochloride, salivary gland hormone and the like have been the typical methods. However, the effect of such therapy is not entirely satisfactory. While instillation of artificial tear and goggle eye patch and the like have been the means to protect the eyes from  
30 drying, these are not more than auxiliary therapy methods.

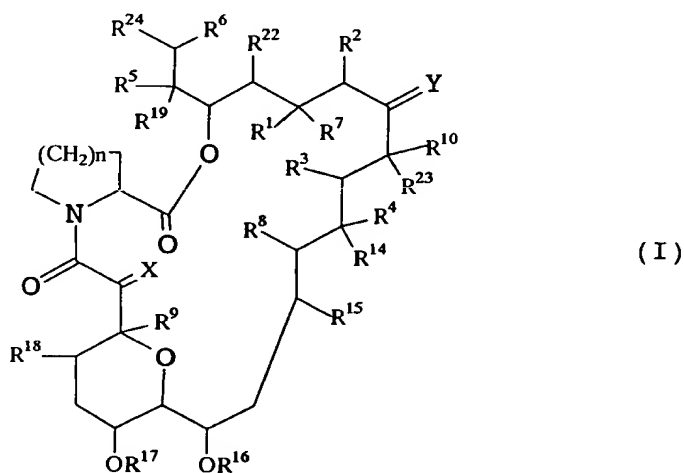
**DISCLOSURE OF THE INVENTION**

As a result of the intensive studies done by the present inventor, it was surprisingly found that a macrolide compound has a superior improving effect on

dry eye symptoms and exhibits a superior therapeutic effect on the dry eye, which resulted in the completion of the present invention.

Accordingly, the present invention provides the following.

- (1) An agent for treating a dry eye, comprising a macrolide compound as an active ingredient.
- (2) The agent of (1), wherein the macrolide compound is a tricyclo compound (I) of the following formula



- wherein adjacent pairs of  $R^1$  and  $R^2$ ,  $R^3$  and  $R^4$ , and  $R^5$  and  $R^6$  each independently
- a) consist of two adjacent hydrogen atoms, wherein  $R^2$  is optionally alkyl, or
  - b) optionally form another bond between carbon atoms binding with the members of said pairs ;
- $R^7$  is hydrogen atom, hydroxy, alkyloxy or protected hydroxy, or may form oxo with  $R^1$  ;
- $R^8$  and  $R^9$  are each independently hydrogen atom or hydroxy ;
- $R^{10}$  is hydrogen atom, alkyl, alkenyl, alkyl substituted by one or more hydroxy, alkenyl substituted by one or more hydroxy, or alkyl substituted by oxo ;
- X is oxo, (hydrogen atom, hydroxy), (hydrogen atom, hydrogen atom), or a group of the formula  $-CH_2O-$  ;
- Y is oxo, (hydrogen atom, hydroxy), (hydrogen atom, hydrogen atom), or a group of the formula  $N-NR^{11}R^{12}$  or  $N-OR^{13}$  ;
- $R^{11}$  and  $R^{12}$  are each independently hydrogen atom, alkyl, aryl or tosyl ;
- $R^{13}$ ,  $R^{14}$ ,  $R^{15}$ ,  $R^{16}$ ,  $R^{17}$ ,  $R^{18}$ ,  $R^{19}$ ,  $R^{22}$  and  $R^{23}$  are each independently hydrogen

atom or alkyl ;

$R^{24}$  is an optionally substituted ring that may contain one or more hetero atom(s) ; and

n is 1 or 2.

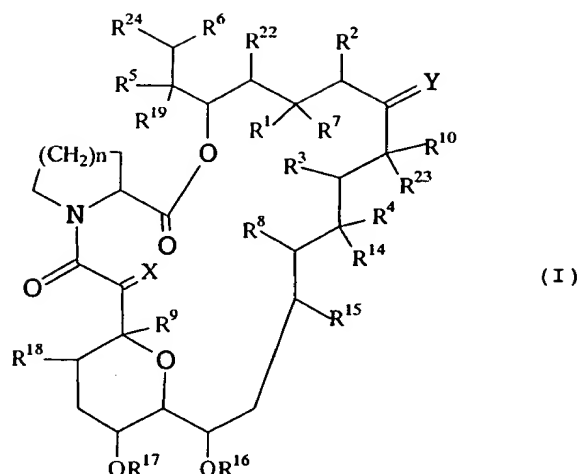
- 5            In addition to the meaning noted above, Y,  $R^{10}$  and  $R^{23}$  may form, together with the carbon atom they bind with, a saturated or unsaturated 5 or 6-membered heterocyclic group containing nitrogen atom, sulfur atom and/or oxygen atom, wherein the heterocyclic group may be substituted by one or more group(s) selected from the group consisting of alkyl, hydroxy, alkyloxy, benzyl, a group of
- 10   the formula  $-CH_2Se(C_6H_5)$ , and alkyl substituted by one or more hydroxy, or a pharmaceutically acceptable salt thereof.
- (3) The agent of (1) or (2), wherein the macrolide compound is FK506.
- (4) The agent of any of (1) to (3), which is in the form of a preparation for local administration to the eye.
- 15   (5) A method for treating dry eye, comprising administering an effective amount of a macrolide compound to a subject in need of the treatment of dry eye.
- (6) Use of a macrolide compound for the production of a pharmaceutical composition for the treatment of dry eye.

Some of the macrolide compounds to be used in the present invention are

20   known as shown below and a novel macrolide compound can be prepared from these known macrolide compounds by a known method. Preferable examples thereof include macrolide compounds such as FK506, Ascomycin derivative, Rapamycin derivative and the like.

Specific examples of macrolide compound include tricyclo compound (I) of

25   the following formula and a pharmaceutically acceptable salt thereof.



wherein adjacent pairs of  $R^1$  and  $R^2$ ,  $R^3$  and  $R^4$ , and  $R^5$  and  $R^6$  each independently

- a) consist of two adjacent hydrogen atoms, wherein  $R^2$  is optionally alkyl, or
- b) optionally form another bond between carbon atoms binding with the members of said pairs ;

5      $R^7$  is hydrogen atom, hydroxy, alkyloxy or protected hydroxy, or may form oxo with  $R^1$  ;

$R^8$  and  $R^9$  are each independently hydrogen atom or hydroxy ;

$R^{10}$  is hydrogen atom, alkyl, alkenyl, alkyl substituted by one or more hydroxy, alkenyl substituted by one or more hydroxy, or alkyl substituted by oxo ;

10      $X$  is oxo, (hydrogen atom, hydroxy), (hydrogen atom, hydrogen atom), or a group of the formula  $-CH_2O-$  ;

$Y$  is oxo, (hydrogen atom, hydroxy), (hydrogen atom, hydrogen atom), or a group of the formula  $N-NR^{11}R^{12}$  or  $N-OR^{13}$  ;

$R^{11}$  and  $R^{12}$  are each independently hydrogen atom, alkyl, aryl or tosyl ;

15      $R^{13}$ ,  $R^{14}$ ,  $R^{15}$ ,  $R^{16}$ ,  $R^{17}$ ,  $R^{18}$ ,  $R^{19}$ ,  $R^{22}$  and  $R^{23}$  are each independently hydrogen atom or alkyl ;

$R^{24}$  is a optionally substituted ring that may contain one or more hetero atom(s) ; and

$n$  is 1 or 2.

20     In addition to the meaning noted above,  $Y$ ,  $R^{10}$  and  $R^{23}$  may form, together with the carbon atom they bind with, a saturated or unsaturated 5 or 6-membered heterocyclic group containing nitrogen atom, sulfur atom and/or oxygen atom, wherein the heterocyclic group may be substituted by one or more group(s)

selected from alkyl, hydroxy, alkyloxy, benzyl, a group of the formula  $-\text{CH}_2\text{Se}(\text{C}_6\text{H}_5)$ , and alkyl substituted by one or more hydroxy.

Preferable  $\text{R}^{24}$  is, for example, cyclo( $\text{C}_5$ - $\text{C}_7$ )alkyl optionally having suitable substituent such as the following.

5 (a) 3,4-dioxocyclohexyl ;

(b) 3- $\text{R}^{20}$ -4- $\text{R}^{21}$ -cyclohexyl,

wherein  $\text{R}^{20}$  is hydroxy, alkyloxy or  $-\text{OCH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3$ , and

$\text{R}^{21}$  is hydroxy,  $-\text{OCN}$ , alkyloxy, heteroaryloxy having suitable substituent,

$-\text{OCH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3$ , protected hydroxy, chloro, bromo, iodo,

10 aminooxalyloxy, azide, p-tolyloxythiocarbonyloxy, or  $\text{R}^{25}\text{R}^{26}\text{CHCOO}-$  (wherein  $\text{R}^{25}$  is hydroxy optionally protected where desired or protected amino, and  $\text{R}^{26}$  is hydrogen atom or methyl,

or  $\text{R}^{20}$  and  $\text{R}^{21}$  in combination form an oxygen atom of epoxide ring) ; or

(c) cyclopentyl wherein cyclopentyl is substituted by methoxymethyl, protected

15 hydroxymethyl where desired, acyloxymethyl (wherein acyl moiety is optionally quaternized dimethylamino where desired or optionally esterified carboxy), one or more optionally protected amino and/or hydroxy, or aminoxalyloxymethyl. Preferable example includes 2-formyl-cyclopentyl.

The definition of each symbol used in the formula (I), specific examples  
20 thereof and preferable embodiments thereof are explained in detail in the following.

"Lower" means that a group has 1 to 6 carbon atoms unless otherwise indicated.

Preferable examples of the alkyl moiety of "alkyl" and "alkyloxy" include linear or branched aliphatic hydrocarbon residue, such as lower alkyl (e.g., methyl,  
25 ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, neopentyl, hexyl and the like).

Preferable examples of "alkenyl" include linear or branched aliphatic hydrocarbon residue having one double bond, such as lower alkenyl (e.g., vinyl, propenyl (e.g., allyl and the like), butenyl, methylpropenyl, pentenyl, hexenyl and the like).

30 Preferable examples of "aryl" include phenyl, tolyl, xylyl, cumenyl, mesityl, naphthyl and the like.

Preferable examples of the protective group for "protected hydroxy" and "protected amino" include 1-(loweralkylthio)(lower)alkyl such as lower



alkylthiomethyl (e.g., methylthiomethyl, ethylthiomethyl, propylthiomethyl, isopropylthiomethyl, butylthiomethyl, isobutylthiomethyl, hexylthiomethyl and the like), with more preference given to C<sub>1</sub> - C<sub>4</sub> alkylthiomethyl and most preference given to methylthiomethyl;

- 5 tri-substituted silyl such as tri(lower)alkylsilyl (e.g., trimethylsilyl, triethylsilyl, tributylsilyl, tert-butyldimethylsilyl, tri-tert-butylsilyl and the like), and lower alkyl-diarylsilyl (e.g., methyldiphenylsilyl, ethyldiphenylsilyl, propyldiphenylsilyl, tert-butyldiphenylsilyl and the like, with more preference given to tri(C<sub>1</sub> - C<sub>4</sub>)alkylsilyl and C<sub>1</sub> - C<sub>4</sub> alkylsilyl, and most preference  
10 given to tert-butyldimethylsilyl, tert-butyldiphenylsilyl;

acyl such as aliphatic acyl derived from carboxylic acid, sulfonic acid and carbamic acid, aliphatic acyl substituted by aromatic acyl and aromatic, and the like.

- The aliphatic acyl is exemplified by lower alkanoyl optionally having 1 or  
15 more suitable substituent(s) (e.g., carboxy) such as formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, carboxyacetyl, carboxypropionyl, carboxybutyryl, carboxyhexanoyl and the like ;  
cyclo(lower)alkyloxy(lower)alkanoyl optionally having one or more suitable substituent(s) (e.g., lower alkyl) such as cyclopropyloxyacetyl, cyclobutyloxy-  
20 propionyl, cycloheptyloxybutyryl, mentyloxyacetyl, mentyloxypropionyl, mentyloxybutyryl, mentyloxypentanoyl, mentyloxyhexanoyl and the like, camphorsulfonyl ;  
lower alkylcarbamoyl having one or more suitable substituent(s) such as carboxy or protected carboxy and the like, such as carboxy(lower)alkylcarbamoyl (e.g.,  
25 carboxymethylcarbamoyl, carboxyethylcarbamoyl, carboxypropylcarbamoyl, carboxybutylcarbamoyl, carboxypentylcarbamoyl, carboxyhexylcarbamoyl) and tri(lower)alkylsilyl(lower)alkyloxycarbonyl(lower)alkylcarbamoyl (e.g., trimethyl-  
silylmethoxycarbonylethylcarbamoyl, trimethylsilylethoxycarbonylpropyl-  
carbamoyl, triethylsilylethoxycarbonylpropylcarbamoyl, tert-butyldimethyl-  
30 silylethoxycarbonylpropylcarbamoyl, trimethylsilylpropoxycarbonylbutyl-  
carbamoyl).

Aromatic acyl is exemplified by aroyl optionally having suitable substituent(s) (e.g., nitro), such as benzoyl, toluoyl, xyloyl, naphthoyl, nitrobenzoyl,

dinitrobenzoyl, nitronaphthoyl and the like ; and  
arenesulfonyl optionally having one or more suitable substituent(s) (e.g., halogen),  
such as benzenesulfonyl, toluenesulfonyl, xylenesulfonyl, naphthalenesulfonyl,  
fluorobenzenesulfonyl, chlorobenzenesulfonyl, bromobenzenesulfonyl,  
5 iodobenzenesulfonyl and the like.

The aliphatic acyl substituted by aromatic group may be, for example,  
ar(lower)alkanoyl optionally having one or more suitable substituent(s) (e.g., lower  
alkyloxy or trihalo(lower)alkyl and the like), wherein specific examples are  
phenylacetyl, phenylpropionyl, phenylbutyryl, 2-trifluoromethyl-2-methoxy-2-  
10 phenylacetyl, 2-ethyl-2-trifluoromethyl-2-phenylacetyl, 2-trifluoromethyl-2-  
propoxy-2-phenylacetyl and the like.

Of the above-mentioned acyl, more preferable acyl includes C<sub>1</sub> - C<sub>4</sub> alkanoyl  
optionally having carboxy, cyclo(C<sub>5</sub> - C<sub>6</sub>)alkyloxy(C<sub>1</sub> - C<sub>4</sub>)alkanoyl having two (C<sub>1</sub> -  
C<sub>4</sub>)alkyl in the cycloalkyl moiety, camphorsulfonyl, carboxy (C<sub>1</sub> - C<sub>4</sub>)alkyl-  
15 carbamoyl, tri(C<sub>1</sub> - C<sub>4</sub>)alkylsilyl(C<sub>1</sub> - C<sub>4</sub>)alkyloxycarbonyl(C<sub>1</sub> - C<sub>4</sub>)alkylcarbamoyl,  
benzoyl optionally having 1 or 2 nitro groups, benzenesulfonyl having halogen,  
and phenyl(C<sub>1</sub> - C<sub>4</sub>)alkanoyl having C<sub>1</sub> - C<sub>4</sub> alkyloxy and trihalo(C<sub>1</sub> - C<sub>4</sub>)alkyl. Of  
these, most preferred are acetyl, carboxypropionyl, mentyloxyacetyl,  
camphorsulfonyl, benzoyl, nitrobenzoyl, dinitrobenzoyl, iodobenzenesulfonyl, 2-  
20 trifluoromethyl-2-methoxy-2-phenylacetyl and the like.

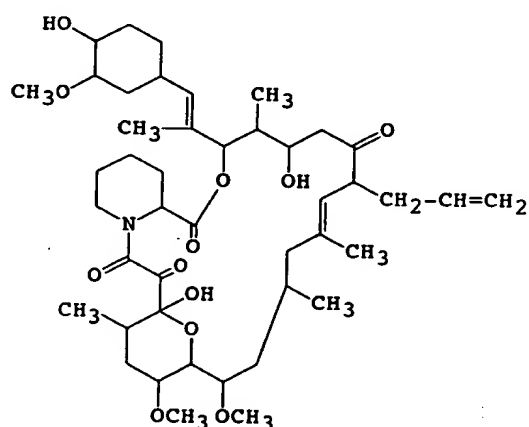
Preferable examples of the "heterocyclic group consisting of saturated or  
unsaturated 5 or 6-membered ring having nitrogen atom, sulfur atom and/or  
oxygen atom" are pyrrolyl, tetrahydrofuryl and the like.

The "heteroaryl optionally having a suitable substituent" moiety of the  
25 "heteroaryloxy optionally having a suitable substituent" is that exemplified for R<sup>1</sup> of  
the compound of the formula I of EP-A-532,088, with preference given to 1-  
hydroxyethylindol-5-yl. The disclosure is incorporated hereinto by reference.

The tricyclo compound (I) and a pharmaceutically acceptable salt thereof  
to be used in the present invention have immunosuppressive action, antibacterial  
30 action and other pharmacological activity, so that they are useful for the  
prophylaxis and treatment of rejection in organ or tissue transplantation, graft  
versus host reaction, autoimmune diseases, infectious diseases and the like, as  
described, together with the production method thereof, in, for example, EP-A-

184162, EP-A-323042, EP-A-423714, EP-A-427680, EP-A-465426, EP-A-480623, EP-A-532088, EP-A-532089, EP-A-569337, EP-A-626385, WO89/05303, WO93/05058, WO96/31514, WO91/13889, WO91/19495, WO93/5059 and the like, all of these publications are hereby incorporated by reference.

- 5 In particular, the compounds called FR900506 (=FK506), FR900520 (Ascomycin), FR900523 and FR900525 are produced by the genus *Streptomyces*, such as *Streptomyces tsukubaensis*, No. 9993 (depository : National Institute of Bioscience and Human-Technology Agency of Industrial Science and Technology, the Ministry of International Trade and Industry, 1-3, Higashi 1-chome,
- 10 Tsukuba-shi, Ibaraki-ken, Japan (formerly : Fermentation Research Institute, Agency of Industrial Science and Technology, the Ministry of International Trade and Industry), date of deposit : October 5, 1984, deposit number : FERM BP-927 or *Streptomyces hygroscopicus subsp. Yakushimaensis*, No. 7238 (depository : National Institute of Bioscience and Human-Technology Agency of Industrial
- 15 Science and Technology, 1-3, Higashi 1-chome, Tsukuba-shi, Ibaraki-ken, Japan (formerly : Fermentation Research Institute, Agency of Industrial Science and Technology, the Ministry of International Trade and Industry), date of deposit : January 12, 1985, deposit number : FERM BP-928 (EP-A-0184162), and the compound of the following formula, FK506 (general name : Tacrolimus), is a
- 20 representative compound.



Chemical name : 17-allyl-1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxy-  
 cyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-  
 11,28-dioxo-4-azatricyclo[22.3.1.0<sup>4,9</sup>]octacos-18-ene-2,3,10,16-tetraone

Of the tricyclo compounds (I), more preferred is a compound wherein adjacent pairs of  $R^3$  and  $R^4$ , and  $R^5$  and  $R^6$  each independently form another bond between carbon atoms binding with the members of said pairs ;

$R^8$  and  $R^{23}$  are each independently hydrogen atom ;

5  $R^9$  is hydroxy ;

$R^{10}$  is methyl, ethyl, propyl or allyl ;

X is (hydrogen atom, hydrogen atom) or oxo ;

Y is oxo ;

$R^{14}$ ,  $R^{15}$ ,  $R^{16}$ ,  $R^{17}$ ,  $R^{18}$ ,  $R^{19}$  and  $R^{22}$  are each independently methyl ;

10  $R^{24}$  is 3- $R^{20}$ -4- $R^{21}$ -cyclohexyl,

wherein  $R^{20}$  is hydroxy, alkyloxy or  $-OCH_2OCH_2CH_2OCH_3$ , and

$R^{21}$  is hydroxy,  $-OCN$ , alkyloxy, heteroaryloxy having suitable substituent,  $-OCH_2OCH_2CH_2OCH_3$ , protected hydroxy, chloro, bromo, iodo, aminooxalyloxy, azide, p-tolyloxythiocarbonyloxy

15 or  $R^{25}R^{26}CHCOO-$  wherein  $R^{25}$  is hydroxy optionally protected when desired, or protected amino, and  $R^{26}$  is hydrogen atom or methyl), or  $R^{20}$  and  $R^{21}$  in combination form an oxygen atom of epoxide ring; and  
n is 1 or 2.

Particularly preferable tricyclo compound (I) includes, besides FK506,  
20 Ascomycin derivatives such as halogenated derivative of 33-epi-chloro-33-desoxy Ascomycin described in Example 66a of EP-A-427,680 and the like.

Other preferable macrolide compounds include Rapamycin described in MERCK INDEX, 12 edition, No. 8288 and derivatives thereof. Preferable examples thereof include O-substituted derivative described at page 1 of  
25 WO95/16691, formula A, wherein the 40<sup>th</sup> hydroxy is  $-OR_1$  (wherein  $R_1$  is hydroxyalkyl, hydroalkyloxyalkyl, acylaminoalkyl or aminoalkyl), such as 40-O-(2-hydroxy)ethyl Rapamycin, 40-O-(3-hydroxy)propyl Rapamycin, 40-O-[2-(2-hydroxy)ethoxy]ethyl Rapamycin and 40-O-(2-acetaminoethyl) Rapamycin.  
These O-substituted derivatives can be produced by reacting, under appropriate  
30 conditions, Rapamycin (or dihydro or deoxo Rapamycin) and an organic radical bound with a leaving group (e.g., RX wherein R is an organic radical desirable as O-substituent, such as alkyl, allyl and benzyl moiety, and X is a leaving group such as  $CCl_3C(NH)O$  and  $CF_3SO_3$ )). The conditions are: when X is  $CCl_3C(NH)O$ ,

acidic or neutral conditions, such as in the presence of trifluoromethanesulfonic acid, camphorsulfonic acid, p-toluenesulfonic acid or their corresponding pyridinium or substituted pyridinium salt, and when X is  $\text{CF}_3\text{SO}_3$ , in the presence of a base such as pyridine, substituted pyridine, diisopropylethylamine and  
5 pentamethyl-piperidine. The most preferable Rapamycin derivative is 40-O-(2-hydroxy)ethyl Rapamycin as disclosed in WO94/09010. The contents of the above references are hereby incorporated into the specification by reference.

The pharmaceutically acceptable salt of tricyclo compound (I), Rapamycin and derivatives thereof are nontoxic and pharmaceutically acceptable  
10 conventional salts, which are exemplified by salts with inorganic or organic base such as alkali metal salt (e.g., sodium salt, potassium salt and the like), alkaline earth metal salt (e.g., calcium salt, magnesium salt and the like), ammonium salt, and amine salt (e.g., triethylamine salt, N-benzyl-N-methylamine salt and the like).

In the macrolide compound of the present invention, conformer or one or  
15 more pairs of stereoisomers, such as optical isomers and geometric isomers, may be included due to asymmetric carbon atom and double bond. Such conformers and isomers are also encompassed in the present invention. In addition, macrolide compounds can form solvates, which case is also encompassed in the present invention. Preferable solvate is exemplified by hydrates and ethanولات.

20 The diseases associated with dry eye in the present invention include those mentioned above inclusive of hypolacrimation, alacrima xerophthalmia, Sjögren syndrome, keratoconjunctivitis sicca, Stevens-Johnson syndrome, ocular pemphigus, marginal blepharitis, diabetes and the like, dry eye observed after cataract operation, that in conjunction with allergic conjunctivitis and the like.

25 The dry eye similar to hypolacrimatioin is also observed, which is caused by VDT work and dry room due to air conditioning and the like.

The treatment agent of the present invention is effective against the above-mentioned dry eye and for the improvement of subjective symptoms, particularly dry eye.

30 The treatment in the context of the present invention includes any management such as prevention, treatment, alleviation of symptom, reduction of symptom, prevention of progression and the like.

The macrolide compound to be used in the present invention can be used

as a pharmaceutical agent for human and animals, and can be administered systemically or locally by oral administration, intravenous administration (inclusive of transfusion), subcutaneous administration, rectal or vaginal administration, administration to local site of the eye (inclusive of eye ointment).

- 5 In consideration of systemic influence, significant expression of the effect and the like, it is particularly preferably used in a form for local administration to the eye.

The dose of the macrolide compound varies depending on the kind, age, body weight of the administration object such as human and animal, condition to be treated, desired therapeutic effect, administration method, treatment period and the like. Generally, when it is administered systemically, the dose is about 10 0.0001 – 1000 mg, preferably 0.001 – 500 mg, which is given in a single dose or 2 to 4 doses a day or in a sustained manner. When it is administered locally to the eye, a preparation containing the active ingredient in a proportion of 0.001 – 10.0 w/v%, preferably 0.005 – 5.0 w/v%, is applied several times a day per eye, 15 preferably instilled or applied 1 to 6 times a day.

According to the present invention, a macrolide compound, which is an active ingredient, can be administered alone or in combination with other pharmacologically active components. When administered after formulating a preparation, it can be administered as a preparation produced by a conventional 20 method. The dosage form may be, for example, eye drop, eye ointment, powder, granule, tablet, capsule, injection, ointment and the like, with particular preference given to eye drop and eye ointment. Such preparation can be produced according to a conventional method. Of such preparations, an oral preparation is preferably a solid solution preparation produced in the same 25 manner as in the preparation of EP-A-0240773. When an eye drop is desired, an eye drop as described in EP-A-0406791 is preferable. When desired, additives generally used for eye drop such as isotonicizing agent (e.g., sodium chloride), buffering agent (e.g., boric acid, sodium-hydrogenphosphate, sodium dihydrogenphosphate and the like), preservative (e.g., benzalkonium chloride, 30 benzetonium chloride, chlorobutanol and the like), tackifier [e.g., sugar (lactose, mannitol, maltose and the like), hyaluronic acid or salt thereof (sodium hyaluronate, potassium hyaluronate and the like), mucopolysaccharide (e.g., chondroitin sulfate and the like), sodium polyacrylate, vinyl carboxy polymer,

crosslinked polyacrylate, and the like] may be added. The contents of the above references in this respect are hereby incorporated into the specification by reference.

The present invention is explained in more detail in the following by way of  
5 Examples, to which the present invention is not limited.

**Examples**

**Example 1**

Using FK506 as the active ingredient in the present invention, a 0.06% eye drop (suspension) having the following formulation was used as a test drug.

10 **test drug**

A suspension having the following formulation and produced in the same manner as in EP-A-0406791 (Example 6).

	FK506	0.6 mg
15	polyvinyl alcohol	7.0 mg
	disodium hydrogenphosphate 12 hydrate	0.05 mg
	sodium dihydrogenphosphate 2 hydrate	0.76 mg
	phosphoric acid	appropriate amount
	sodium hydroxide	appropriate amount
20	sodium chloride	8.56 mg
	benzalkonium chloride	0.1 mg
	injectable water	appropriate amount
Total amount		1 ml

25 The above-mentioned test drug was consecutively administered twice a day for two weeks to a male (44 years old) having subjective symptoms of dry eye (sense of dryness, foreign matter and grittiness) and, as a result, the subjective symptoms disappeared.

From the above result, the test drug was confirmed to be effective for the  
30 improvement of subjective symptoms of dry eye.

**Industrial applicability**

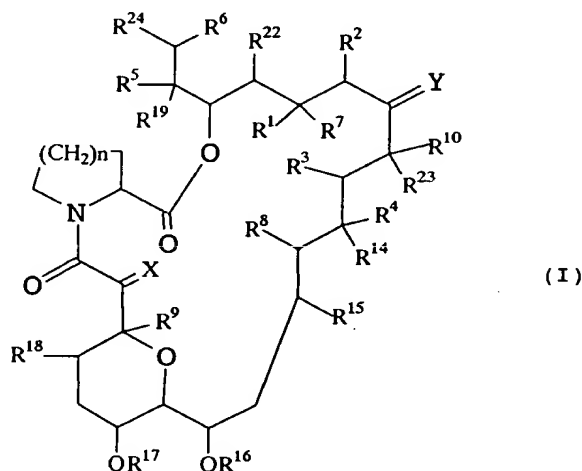
The treatment agent of the present invention, which comprises a

macrolide compound as an active ingredient, has superior improving effect against dry eye, particularly the subjective symptoms of dry eye. Therefore, the treatment agent of the present invention is suggested to be useful as an agent for treating dry eye.



# WHAT IS CLAIMED IS

1. An agent for treating a dry eye, comprising a macrolide compound as an active ingredient.
2. The agent of claim 1, wherein the macrolide compound is a tricyclo compound (I) of the following formula



- wherein adjacent pairs of  $R^1$  and  $R^2$ ,  $R^3$  and  $R^4$ , and  $R^5$  and  $R^6$  each independently
- a) consist of two adjacent hydrogen atoms, wherein  $R^2$  is optionally alkyl, or
  - b) optionally form another bond between carbon atoms binding with the members of said pairs ;
- $R^7$  is hydrogen atom, hydroxy, alkyloxy or protected hydroxy, or optionally form oxo with  $R^1$  ;
- $R^8$  and  $R^9$  are each independently hydrogen atom or hydroxy ;
- $R^{10}$  is hydrogen atom, alkyl, alkenyl, alkyl substituted by one or more hydroxy, alkenyl substituted by one or more hydroxy, or alkyl substituted by oxo ;
- $X$  is oxo, (hydrogen atom, hydroxy), (hydrogen atom, hydrogen atom), or a group of the formula  $-CH_2O-$  ;
- $Y$  is oxo, (hydrogen atom, hydroxy), (hydrogen atom, hydrogen atom), or a group of the formula  $N-NR^{11}R^{12}$  or  $N-OR^{13}$  ;
- $R^{11}$  and  $R^{12}$  are each independently hydrogen atom, alkyl, aryl or tosyl ;
- $R^{13}$ ,  $R^{14}$ ,  $R^{15}$ ,  $R^{16}$ ,  $R^{17}$ ,  $R^{18}$ ,  $R^{19}$ ,  $R^{22}$  and  $R^{23}$  are each independently hydrogen atom or alkyl ;

R<sup>24</sup> is a ring that is optionally substituted and optionally contains one or more hetero atom(s) ; and

n is 1 or 2,

5        wherein Y, R<sup>10</sup> and R<sup>23</sup> optionally form, together with the carbon atom they  
bind with, a saturated or unsaturated 5 or 6-membered heterocyclic  
group containing nitrogen atom, sulfur atom and/or oxygen atom, the  
heterocyclic group being optionally substituted by one or more group(s)  
selected from the group consisting of alkyl, hydroxy, alkyloxy, benzyl, a  
group of the formula -CH<sub>2</sub>Se(C<sub>6</sub>H<sub>5</sub>), and alkyl substituted by one or more  
10        hydroxy,  
or a pharmaceutically acceptable salt thereof.

3. The agent of claim 1 or claim 2, wherein the macrolide compound is FK506.
- 15    4. The agent of any of claim 1 to claim 3, which is in the form of a preparation for local administration to the eye.
5. A method for treating dry eye, comprising administering an effective amount of macrolide compound to a subject in need of the treatment of dry eye.
- 20    6. Use of a macrolide compound for the production of a pharmaceutical composition for the treatment of dry eye.

# **ABSTRACT OF THE DISCLOSURE**

The present invention provides an agent for treating dry eye, which contains a macrolide compound such as FK506.



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